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Genetic Testing for Angelman Syndrome

Information for Patients and Families

What is Angelman syndrome?
Angelman syndrome is a rare genetic condition. Common findings include: developmental delay, speech problems, small head size (microcephaly), movement or balance disorders, abnormal electrical activity of the brain (EEG), and seizures. Individuals with Angelman syndrome can also have frequent laughter and a happy attitude. It is important to remember that there is a lot of variability in the features of individuals with Angelman syndrome. Not everyone with this condition has all of the features or is affected to the same degree of severity.

What causes Angelman syndrome?
There are several causes of Angelman syndrome.
- Deletion: About 70-75% of people with Angelman syndrome are missing a segment of chromosome 15. Chromosomes are structures that carry our genes. This missing part of the chromosome happens by accident when the egg and sperm come together. Thus, there is very little chance (<1%) that this will happen again in a family.
- Paternal UPD: About 2-5% of people with Angelman syndrome got two copies of chromosome 15 from their dad and did not get any copy of chromosome 15 from their mom. This is called paternal UPD and also happens by accident when the egg and sperm come together. Thus, there is very little chance (<1%) that this will happen again in a family.
- Imprinting problems: About 2-5% of people with Angelman syndrome have an imprinting problem. Some areas of chromosome 15 are in charge of turning genes on and off. Genes are the instructions that make proteins in our body. An imprinting problem means that genes on chromosome 15 are not turned on and off properly. This can sometimes run in a family, so there may be up to a 50% recurrence risk.
- *UBE3A* mutations: About 5-10% of patients with Angelman syndrome have a change in the *UBE3A* (ubiquitin-protein ligase E3A) gene. When there is a change (mutation) in the gene, the protein may not be working properly, causing the features in Angelman syndrome. This can also sometimes run in a family, so there may be up to a 50% recurrence risk.
- Unknown cause: About 10-15% of people with Angelman syndrome do not have the above problems. Research continues to look for other causes of Angelman syndrome to explain these cases.

Can my child be tested? Can I be tested? Can my family members be tested?
The first person to be tested in any family should be the individual thought to have Angelman syndrome. Because there are many causes of Angelman syndrome, testing is complex. MS-MLPA is a test that will be positive in people with a deletion, paternal UPD or imprinting problems. If MS-MLPA is positive, it will also tell whether the person has a large deletionor a deletion of only the imprinting center. If MS-MLPA is positive, but the person does not have one of these deletions, UPD15 testing is next. If MS-MLPA is negative, testing of the *UBE3A* gene is next. Once a change is found in someone with Angelman syndrome, other family members may be tested for the same change.

Reasons for genetic testing for CdLS:
- confirm the diagnosis
- reassure that other family members are not affected
- provide information and resources for future pregnancies
- provide information during a pregnancy regarding possible Angelman syndrome in the baby

What does it mean for my child if they find a change? What does it mean for our family?
Finding a change will confirm that the child has Angelman syndrome. Knowing how your child got Angelman syndrome will also tell you the chances of having a second child or other family members with Angelman

syndrome. Once a change has been found in an individual, then other family members may be tested, if they choose to.

What does it mean for my child if they don't find a change?
Not finding a change does not mean that your child does not have Angelman syndrome. If your doctor is not sure about the diagnosis, a negative result may lean against it. We are only able to find changes in about 85% of people with Angelman syndrome. Researchers are working to improve our testing.

What does it mean for my child if they find a variant of unknown significance?
A small number of patients will be found to have a change in the gene, but we are not sure whether that change causes Angelman syndrome or not. In this situation, we recommend testing parents to learn more about the change.

How do I get my child tested?
We suggest that a genetic doctor or genetic counselor help you order the test for your child. If you think your child may have Angelman syndrome, you should make an appointment with someone that works in genetics. This can be made through your local physician or hospital. They can order the testing for Angelman syndrome. If there are any questions about ordering the testing, please ask them to contact The University of Chicago Genetics Services Laboratory. A blood sample is required for testing. UPD15 testing also requires a blood sample from each parent.

How much does the testing cost and will my child's health insurance cover it?
Cost for MS-MLPA is $525, cost for UPD15 is $540, and cost for *UBE3A* testing is $2025 for sequencing and $1000 for deletion/duplication analysis. All insurance companies are different, but most of them should cover at least part of the cost of testing. You can contact your insurance company to learn more about your coverage prior to testing. You will want to ask your insurance company what your coverage is for the following CPT (Current Procedural Terminology) codes:
- MS-MLPA: 81331
- UPD15 testing: 81402
- UBE3A sequencing: 81406
- UBE3A deletion/duplication analysis: 81405

Insurance companies use these codes to define how the testing is done. The University of Chicago or your hospital or lab will bill your child's insurance company. You may receive a bill for any amount not covered by your insurance company. If you do not have medical insurance, you will need to pay by check or credit card before the lab will start testing.

When/how will I get the results?
Testing takes approximately 2-4 weeks for MS-MLPA and UPD15 and 4-6 weeks for *UBE3A* sequencing. Your physician will get the results by fax as soon as testing is done.

Additional Resources:
Angelman Syndrome Foundation
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